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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO
09/938,689	08/23/2001	Manley Huang	9342-028	3530

20583 7590 03/27/2003

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EXAMINER	
NGUYEN, QUANG	

ART UNIT	PAPER NUMBER
1636	11

DATE MAILED: 03/27/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/938,689	HUANG ET AL.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cov r sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) *1-16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-28 are pending in the present application.

Applicants' election without traverse the invention of Group IV (claims 17-28) in Paper No. 10 is acknowledged.

Accordingly, claims 1-16 are withdrawn from further consideration because they are drawn to non-elected inventions.

Claims 17-28 are examined on the merits herein.

Claim Objections

Claim 28 is objected to because of the following informalities: the term "Drab" is not properly written. It should be - - DRab - -. Appropriate correction is required.

Written Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 17-28 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the

filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1117. The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1116.

Applicant's invention is drawn to a recipient mouse comprising a disruption in both alleles of a gene such that lymphocyte maturation does not occur; and a human transgene comprising a nucleic acid molecule that encodes a MHC Class II DR3 molecule, wherein the transgene comprises naturally linked DRab and DQab alleles. Applicants' invention is also drawn to a method of making a recipient mouse, said method comprising: disrupting both alleles of a gene so that lymphocyte maturation does not occur; inserting a transgene comprising nucleic acid that encodes MHC Class II DR3 and DQ2 molecules, wherein the DRab and DQab alleles are naturally linked; and inactivating murine I-Eα; as well as a method of making a recipient mouse, said method comprising: preventing VDJ recombination by mutating both alleles of the RAG-2 gene; inserting a transgene comprising the DRab and DQab alleles of the MHC Class II DR3 halotype; and inactivating murine I-Eα. The instant claims encompass a recipient mouse comprising a disruption in both alleles of any gene involved in lymphocyte maturation, and said mouse contains a human transgene comprising a nucleic acid sequence encoding a MHC Class II DR3 molecule, wherein the transgene comprises naturally linked DRab and DQab alleles, and the mouse has any phenotype, and any methods of making the same transgenic recipient mouse. However, apart from

the disclosure of making 4D1/C2D/RAG-2 mice (presumably via breeding between 4D1/CD2 double transgenic mice with RAG-2 mice) that express surface DR and not I-Eα, and wherein the mice appear to have a functional intact immune response (e.g., eliciting T-cell and antibody responses), the instant specification fails to teach a representative number of species of claimed transgenic recipient mice having a disruption of both alleles of any gene involved in lymphocyte maturation and having any phenotype as encompassed by the scope of the instant claims, and any methods for making the same transgenic recipient mice. The state of the art at the filing date of the present application does not provide such guidance, particularly the state of transgenesis is known to be highly unpredictable with respect to the attainment of any desired phenotype. The claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification and which are not conventional in the art as of Applicants' filing date. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). The skilled artisan cannot envision the detailed structure of a transgenic recipient mouse as broadly claimed and broadly claimed methods for making the same, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention

and reference to a potential method of isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991). One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 112

Claims 17-28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a recipient mouse whose genome comprises a disruption in both alleles of the RAG-2 gene, and a human transgene comprising a nucleic acid sequence that encodes a MHC Class II DR molecule, wherein the transgene comprises naturally linked DRab and DQab alleles; and a method of making the same recipient mouse, said method comprises the introduction of said human transgene into a transgenic mouse whose genome comprises a disruption in both alleles of the RAG-2 gene in a backgound deficient for murine I-Eα through breeding;

does not reasonably provide enablement for a recipient mouse comprising a disruption in both alleles of any gene involved in lymphocyte maturation, and containing a human transgene comprising a nucleic acid sequence that encodes a MHC Class II DR molecule, wherein the transgene comprises naturally linked DRab and DQab alleles with any phenotype; and any method for making the same recipient mouse. The

specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte Forman*, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

Claims 17-21 are drawn to a recipient mouse comprising a disruption in both alleles of a gene such that lymphocyte maturation does not occur; and a human transgene comprising a nucleic acid molecule that encodes a MHC Class II DR3 molecule, wherein the transgene comprises naturally linked DRab and DQab alleles; the same with the various limitation recited in the dependent claims.

Claims 22-27 are drawn to a method of making a recipient mouse, said method comprising: disrupting both alleles of a gene so that lymphocyte maturation does not occur; inserting a transgene comprising nucleic acid that encodes MHC Class II DR3 and DQ2 molecules, wherein the DRab and DQab alleles are naturally linked; and inactivating murine I-Eα.

Claim 28 is drawn to a method of making a recipient mouse, said method comprising: preventing VDJ recombination by mutating both alleles of the RAG-2 gene;

inserting a transgene comprising the DRab and DQab alleles of the MHC Class II DR3 halotype; and inactivating murine I-Eα.

With respect to the elected invention, the specification teaches by exemplification showing the attainment of 4D1/C2D/RAG-2 mice (presumably via breeding between 4D1/CD2 double transgenic mice with RAG-2 mice) that express surface DR and not I-Eα, and wherein the mice appear to have a functional intact immune response (e.g., eliciting T-cell and antibody responses; see pages 42-46).

The above evidence has been noted and considered. However, the evidence is not reasonably extrapolated to the instant broadly claimed invention for the reasons discussed below.

(a) *The breadth of the claims*. The instant claims encompass the making of a recipient mouse whose genome comprises a disruption in both alleles of any gene that is involved in lymphocyte maturation, and said mouse contains a human transgene comprising a nucleic acid sequence encoding a MHC Class II DR3 molecule, wherein the transgene comprises naturally linked DRab and DQab alleles, and the mouse has any phenotype, and any methods of making the same transgenic recipient mouse using any material for disrupting both alleles of a gene involved in lymphocyte maturation, for inserting a transgene comprising nucleic acid sequence encoding a MHC Class II DR3 molecule, wherein the DRab and DQab alleles are naturally linked and for inactivating murine I-Eα. The method claims also encompass the concurrent introduction of nucleic acid sequences for disrupting both alleles of a gene involved in lymphocyte maturation, for inserting a transgene comprising nucleic acid sequence encoding a MHC Class II

DR3 molecule, wherein the DRab and DQab alleles are naturally linked and for inactivating murine I-Eα into an embryonic stem cell for the generation of the recipient mouse.

(b) The state and the unpredictability of the prior art. At the filing date of the present application, the art of transgenesis was known to be highly unpredictable with respect to the unpredictability of the incorporation and expression of the transgenes as well as the knockout of any genes to attain any desired phenotype in any animal species as a result of such modification(s). It should be noted that the level and specificity of the specific transgene (for this instance a human transgene encoding a MHC Class II DR3 molecule, wherein the transgene comprising naturally linked DRab and DQab alleles) as well as the resulting phenotype of the transgenic mouse are directly dependent on the specific transgene construct. The individual gene of interest, promoter, enhancer, coding or non-coding sequences present in the transgene construct, the specificity of transgene integration into the genome are all important factors in controlling the expression of a transgene in the production of transgenic animal which exhibits a resulting phenotype. This observation is supported by Wall (Theriogenology 45:57-68, 1996) who states that "[o]ur lack of understanding of essential genetic control elements makes it difficult to design transgenes with predictable behavior" (page 61, last paragraph). Moreadith et al. (J. Mol. Med. 75:208-216, 1997) supports phenotypic unpredictability in knockout mice. In particular, Moreadith et al. discuss that gene targeting at a particular locus is unpredictable with respect to the resulting phenotype since often the generation of knockout mice, in many

instances, changes the prevailing notions regarding the functions of the encoded proteins. For example, Moreadith et al. report that gene targeting at the endothelial loci led to the creation of mice with Hirschsprung's disease instead of the anticipated phenotype of abnormal control of blood pressure (See page 208, column 2, second paragraph). The unpredictability of the resulting phenotypes for HLA transgenic mice is also supported by recent results of Chen et al. (J. Immunol. 168:3050-3056, 2002) and Chen et al. (Eur. J. Immunol. 33:172-182, 2003). Using a large 550kb YAC construct encompassing both HLA-DR3/DQ2, the HLA DR3/DQ2 transgenic mice in an I-Aβ° background of Chen et al. (Eur. J. Immunol.) show DR expression in resting or activated T lineage cells whereas the HLA DR3-DQ2 transgenic mice in the same background generated from a shorter 320kb construct by Chen et al. (J. Immunol.) do not.

(c) The amount of direction or guidance provided. In light of the state of the prior art at the filing date of the present application, the instant specification is not enabled for the presently broadly claimed invention. This is because apart from the exemplification showing the attainment of 4D1/C2D/RAG-2 mice in the I-Aβ° background (presumably via breeding between 4D1/CD2 double transgenic mice with RAG-2 mice) that express surface DR and not I-Eα, and wherein the mice appear to have a functional intact immune response (e.g., eliciting T-cell and antibody responses; see pages 42-46), it is unclear whether the same phenotype, let alone any phenotype (and what are the use of other undisclosed phenotype(s)?) could be obtained for a transgenic recipient mouse where both alleles of any gene involved in the lymphocyte maturation are disrupted. The instant specification also does not provide sufficient guidance for a skilled artisan

on how to obtain the recipient mouse as claimed using any methods with any materials as long as both alleles of a gene involved in lymphocyte maturation are disrupted, the murine I-Eα is inactivated and the human transgene encoding a MHC Class II DR3 molecule, wherein the transgene contains naturally linked DRab and DQab alleles is inserted. Therefore, in the absence of sufficient guidance provided by the instant disclosure, it would have required undue experimentation for a skilled artisan to make and use the full scope of the presently claimed invention. The physiological art is recognized as unpredictable (MPEP 2164.03). Particularly, it is already noted by Applicants that unlike RAG-1 and TCRβ/δ_mutant mice, $RAG2^{-/-}$ mouse strain confers a unique support for the functional development of allogeneic HSC without any radiation, and that SCID mice are not able to support functional development of allogeneic HSC (see Table 2). As set forth in *In re Fisher*, 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> That scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the are; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

With the lack of sufficient guidance provided by the present disclosure, it would require undue experimentation for a skilled artisan to make and use the instant broadly claimed invention.

As written the claims also encompass an embodiment wherein the human MHC Class II DR3 transgene is not necessarily incorporated into the genome of the transgenic recipient mouse. The instant specification is not enabled for such a broadly

claimed invention. This is because apart from the teachings of introducing the human HLA transgene into an ES cell, and making the transgenic recipient mouse through breeding with known RAG2 and I-Eα deficient mouse strains, the present disclosure fails to provide any guidance for a skilled artisan how to make and use the aforementioned embodiment. It is already well known in the art, particularly in the art of *in vivo* nucleic acid application, that transgene expression *in vivo* is very transient. It is also unclear whether introducing the human HLA transgene by any route of administration into a recipient mouse, an effective level of the HLA transgene could be generated and maintained for a sufficient period of time to yield any desired phenotype. Therefore, with the lack of sufficient guidance provided by the instant specification, it would have required undue experimentation for a skilled artisan to make and use the full scope of the presently claimed invention.

Accordingly, due to the lack of sufficient guidance provided by the specification regarding to the issues set forth above, the unpredictability of the transgenic and physiological arts in general, and the breadth of the claims, it would have required undue experimentation for one skilled in the art to make and use the instant broadly claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 22-28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 22-28 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential essential components and/or essential steps. As written, it is unclear how both alleles of a gene involved in lymphocyte maturation (e.g., RAG-2 gene) are disrupted and in which cells the disruption is carried out; and how a transgene comprising a nucleic acid that encodes MHC Class II DR3 and DQ2 molecules, wherein the DRab and DQab alleles are naturally linked is inserted and in which cells; and how murine I-Eα is inactivated to make the recipient mouse as claimed. The metes and bounds of the claims are not clearly determined.

Conclusions

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, Gerald Leffers, Jr., Ph.D., may be reached at (703) 305-6232, or SPE, Remy Yucel, Ph.D., at (703) 305-1998.

Quang Nguyen, Ph.D.

PATENT EXAMINER
Gerald G. Leffers Jr.
A.U. 1636